

EVALUATION OF PROGNOSTIC FACTORS IN
WILMS TUMOUR



Dissertation submitted to
Coimbatore Medical College & Hospital,
Coimbatore

For
M.Ch. – Paediatric Surgery
Branch V



The Tamil Nadu
Dr. M. G. R. Medical University
Chennai
AUGUST – 2010

CERTIFICATE

This is to certify that the dissertation entitled “**EVALUATION OF PROGNOSTIC FACTORS IN WILMS TUMOUR**” is a bonafide record of the work done by **Dr. R.P.DHARMENDRA**, under my guidance and supervision in the Department of Paediatric Surgery during the period of his Post Graduate study at Coimbatore Medical College, Coimbatore for the degree of M.Ch. Paediatric Surgery (Branch V) from 2007 - 2010.

Professor and Head

Dept. of Paediatric Surgery

Coimbatore Medical College Hospital

Dean

Coimbatore Medical College Hospital

DECLARATION

I solemnly declare that the dissertation titled “**EVALUATION OF PROGNOSTIC FACTORS IN WILMS TUMOUR**” has been prepared by me.

This is submitted to the **Tamilnadu Dr.M.G.R.Medical University**, Chennai in partial fulfillment of the requirements for the award of M.Ch. Paediatric Surgery (Branch V) to be held in August 2010.

Place: Coimbatore

Date:

Dr.R.P.DHARMENDRA

ACKNOWLEDGEMENT

I wish to record my sincere thanks to our **Prof.V.KUMARAN, M.S.,M.Ch., DEAN** Coimbatore Medical College Hospital, Coimbatore for permitting me to work for this Dissertation and to avail all the facilities in this Institution.

I am deeply indebted to our **Prof.V.KUMARAN, M.S., M.Ch.,** Professor and Head of the Department of Paediatric Surgery, Coimbatore Medical College Hospital, Coimbatore, but for whose guidance, this study would not have come through. It has been a great privilege to work under him and especially on this topic.

I express my profound gratitude to **Dr.G.RAJAMANI, Dr.S.KANNAN, Dr.N.VENKATESA MOHAN, Dr.M.NATARAJ, Dr.V.MUTHULINGAM, Dr.L.SENTHIL KUMAR, Dr.CHITRA RAMU** for their generous help, advice and suggestions in various stages of this study.

This study would not have seen the light of the day, had not our patients showed the kind co-operation they extended. I sincerely thank them.

CONTENTS

Chapter No.	Title	Page No.
1.	INTRODUCTION	1
2.	AIMS OF THE STUDY	3
3.	MATERIALS AND METHODS	4
4.	RESULTS	8
5.	REVIEW OF LITERATURE	15
6.	DISCUSSION	49
7.	CONCLUSION	57
8.	BIBLIOGRAPHY	
9.	PROFORMA	
10.	MASTER CHART	

INTRODUCTION

Wilms tumour (WT) is the most common renal tumor of childhood typically affects children under the age of 6 years. The overall annual incidence of Wilms' tumor is approximately 7.6 cases per million children under 15 years of age. Wilms' tumor accounts for 6–7% of all childhood cancers. It is the subject of intense academic interest due to its occurrence in paediatric age group with significant mortality.

This has been significantly reduced with relapse free survival rates due to ongoing scientific research and various cooperative protocols like National Wilms Tumour Study Group(NWTSG), Society for International Paediatric oncology group(SIOP), United Kingdom Children Cancer Study Group(UKCCSG).

New treatment protocols with addition of chemotherapy and radiotherapy have contributed in improving the survival especially in the low risk Wilms tumour.

Unfortunately patients with unfavourable histology, lung, liver metastasis, major tumour spillage and bilateral tumours have worst outcome.

The present study is to analyse the various prognostic factors that determines the outcome of Wilms tumour and to analyse the prognostic significance of tumour staging and histopathology in Wilms tumour patients treated at our hospital.

AIMS OF THE STUDY

1. To assess the various prognostic factors that determines the outcome of Wilms tumour.
2. To analyze the prognostic value of histopathology in Wilms tumour.
3. To analyze the prognostic significance of tumour staging in Wilms tumour.
4. To identify the causes for early mortality in Wilms tumour.

MATERIAL AND METHODS

Study design:

It is retrospective and prospective study evaluating the various prognostic factors that determines the outcome of Wilms tumour in our hospital.

Study Period:

December 1999 to December 2009

Study Centre:

Department of Paediatric surgery , Coimbatore Medical College, Coimbatore.

Inclusion Criteria:

- All patients with Wilms tumour admitted between December 1999 to December 2009 were included in this study.
- Age group – 0 to 12 Years.

Exclusion Criteria:

- Two cases of Wilms tumour who expired before starting the treatment were excluded from this study.

METHODOLOGY

All the patients with renal mass admitted in our department was evaluated thoroughly by clinical examination and the following investigations.

Laboratory Studies

- Complete blood count
- Basic metabolic panel, including serum calcium levels
- Coagulation abnormalities (to rule out acquired von Willebrand disease, which is coincident in up to 8% of individuals with Wilms tumor)
- Liver function tests
- Renal function tests
- Urinalysis and urine culture

Imaging Studies

- Ultrasonography
 - Initial diagnosis of a renal or abdominal mass, possible renal vein or inferior vena cava (IVC) thrombus (Doppler flow study may be helpful in the setting of vascular invasion.)

- Information regarding liver and other kidney
- CT scanning of the chest and abdomen
 - Differential diagnosis of a kidney tumor versus adrenal tumor (neuroblastoma)
 - Liver metastases
 - Status of opposite kidney
 - Lymph node assessment
 - Status of chest with respect to metastases
- Chest radiography - As a baseline for pulmonary metastases
- Magnetic resonance imaging
 - Typically, these tumors appear inhomogeneous on gadolinium-enhanced MRI, while the nephrogenic rests (which sometimes are precursors of Wilms tumor [WT]) appear as homogeneous masses.
 - MRI is also useful for magnetic resonance venography to aid in the diagnosis of thrombus of the renal vein of the IVC.
 - MRI scanning of the head is recommended in patients with suspected rhabdoid and clear cell carcinoma of the kidney.

All following datas relating to the patients and the biological characteristics of the tumour were obtained from case records.

These information were recorded on a separate proforma that was designed specifically for this study.

- Age
- Gender
- Histopathology – Favourable and unfavourable
- Tumour spillage
- Microscopic involvement of surgical margins
- Abdominal lymph node involvement
- Tumour thrombus involving the Inferior Vena Cava

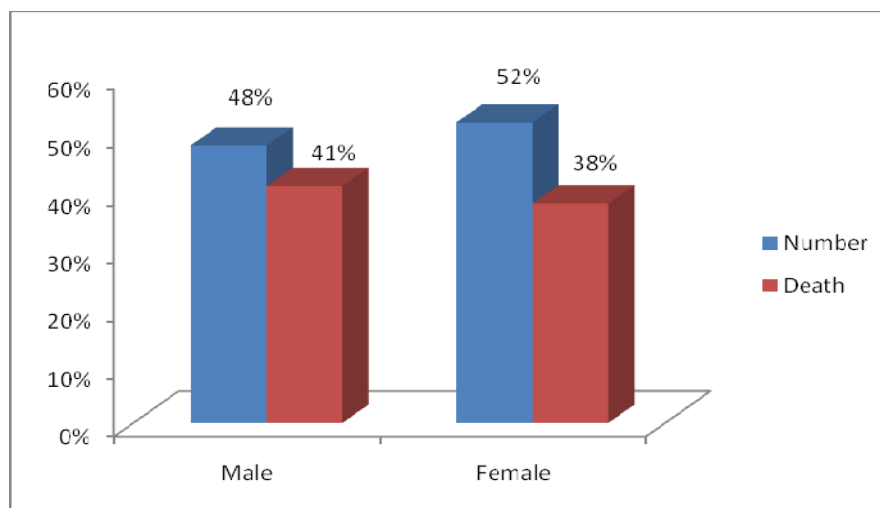
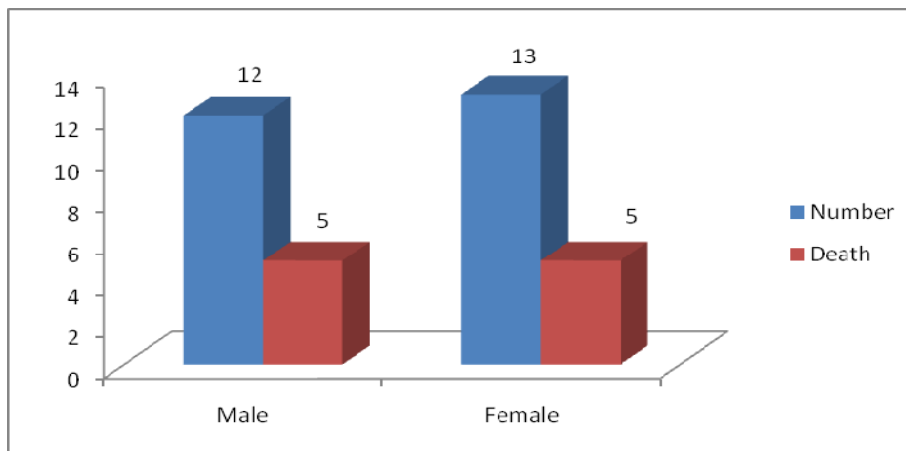
Staging was assessed according to the system used by the recent NWTSG protocol.

RESULTS

Hospital charts and surgical notes were reviewed and the results of 25 children with Wilms tumour were analyzed.

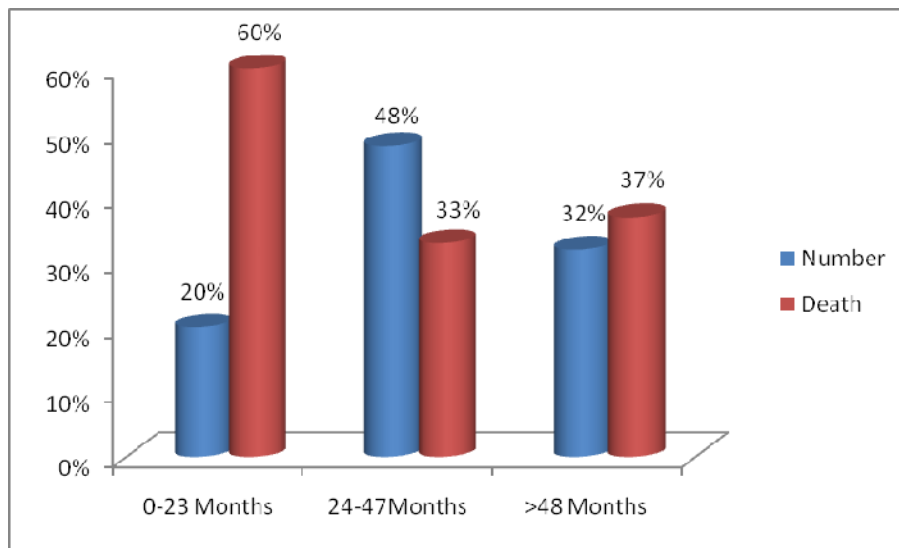
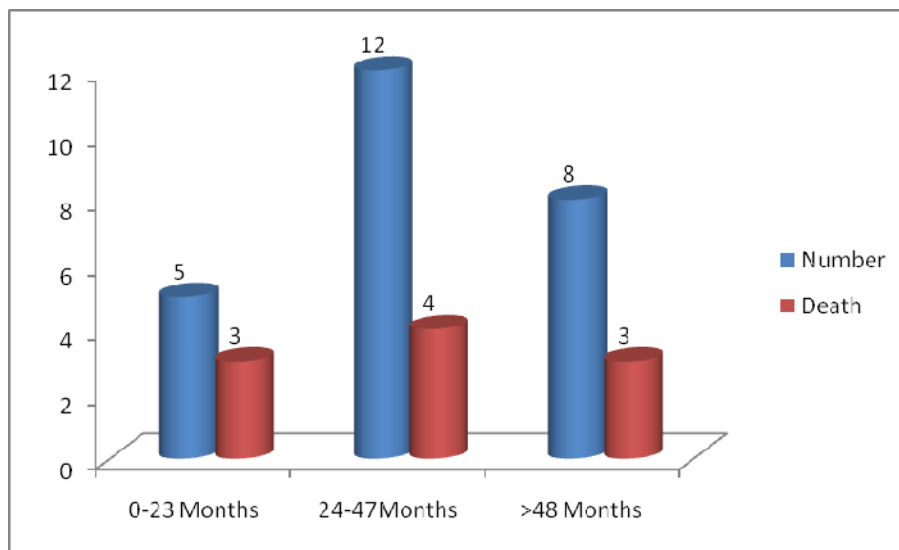
Gender:

	Number	Percentage	Death	Percentage
Male	12	48%	5	41%
Female	13	52%	5	38%



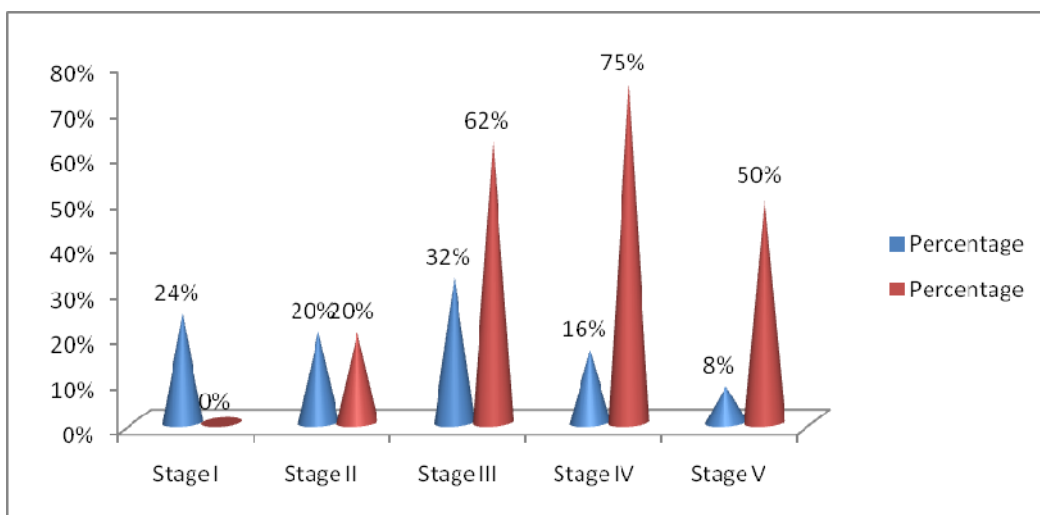
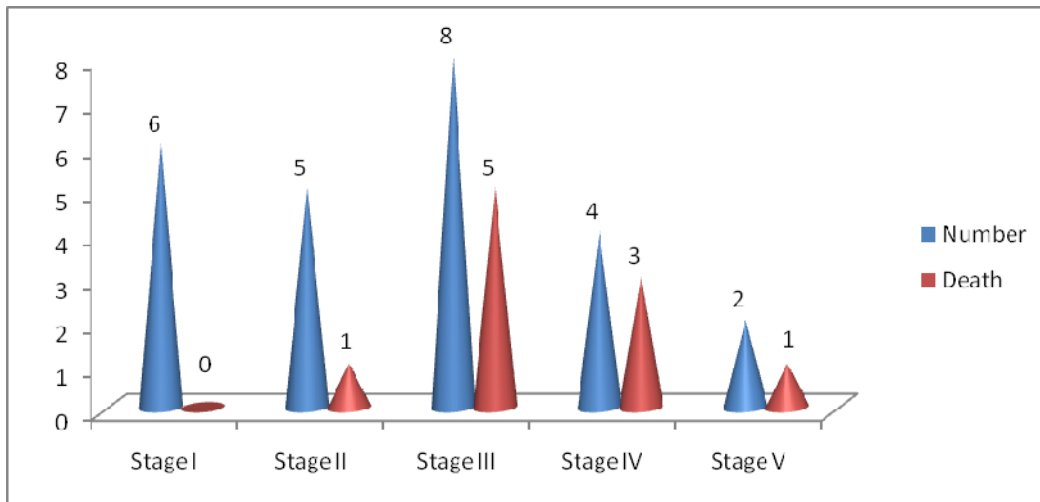
Age Group:

	Number	Percentage	Death	Percentage
0-23 Months	5	20%	3	60%
24-47Months	12	48%	4	33%
>48 Months	8	32%	3	37%



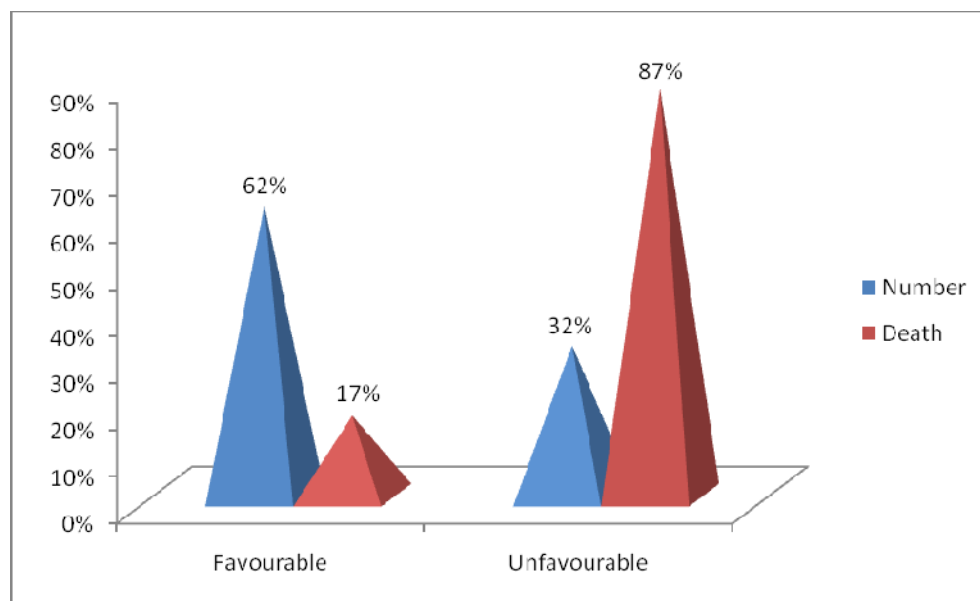
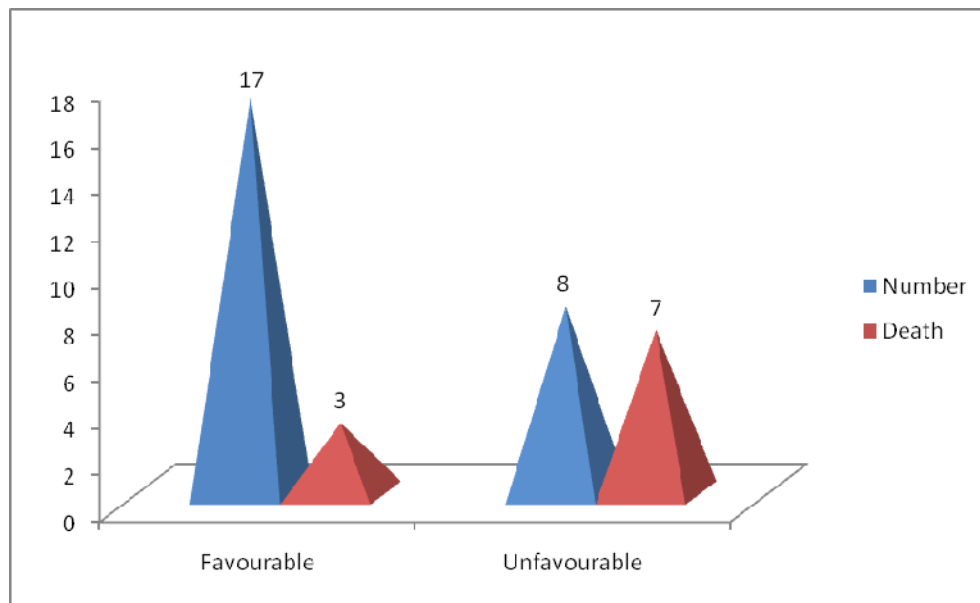
Staging

	Number	Percentage	Death	Percentage
Stage I	6	24%	-	0%
Stage II	5	20%	1	20%
Stage III	8	32%	5	62%
Stage IV	4	16%	3	75%
Stage V	2	8%	1	50%



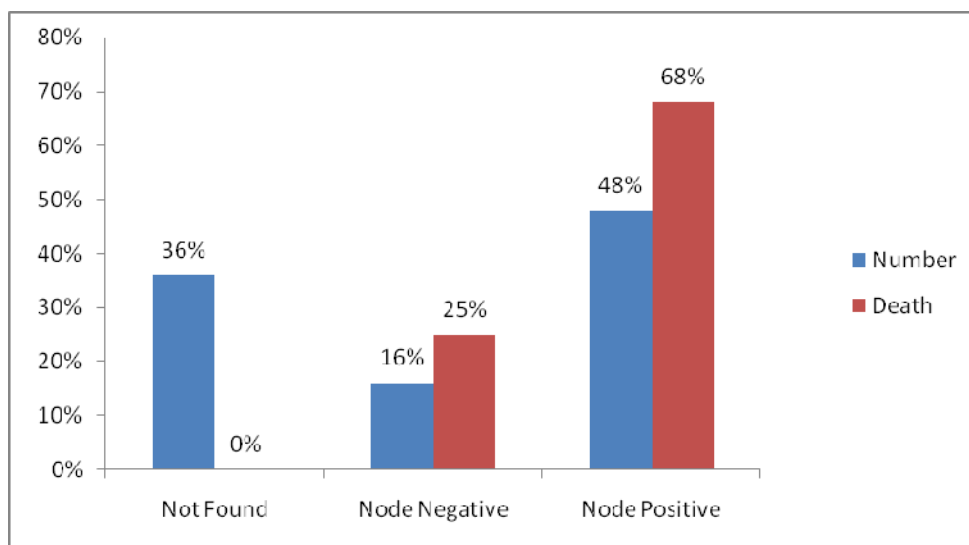
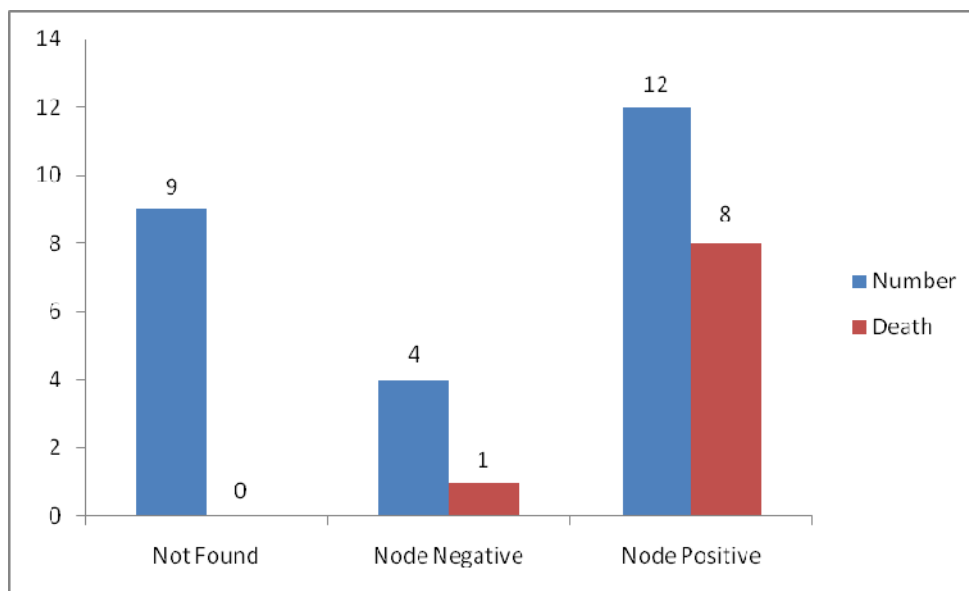
Histopathology

	Number	Percentage	Death	Percentage
Favourable	17	62%	3	17%
Unfavourable	8	32%	7	87%



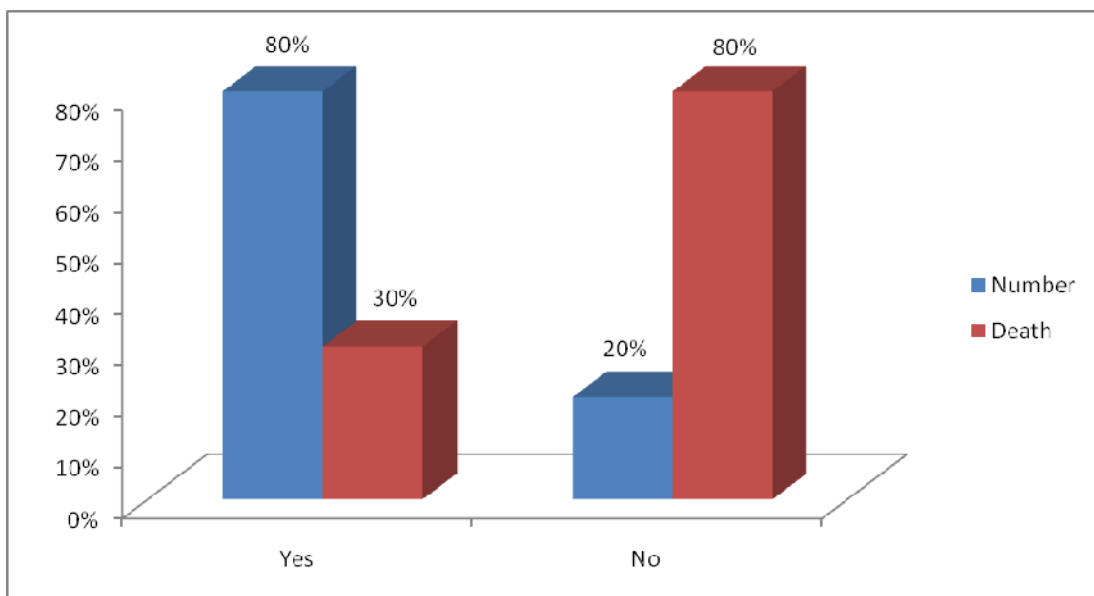
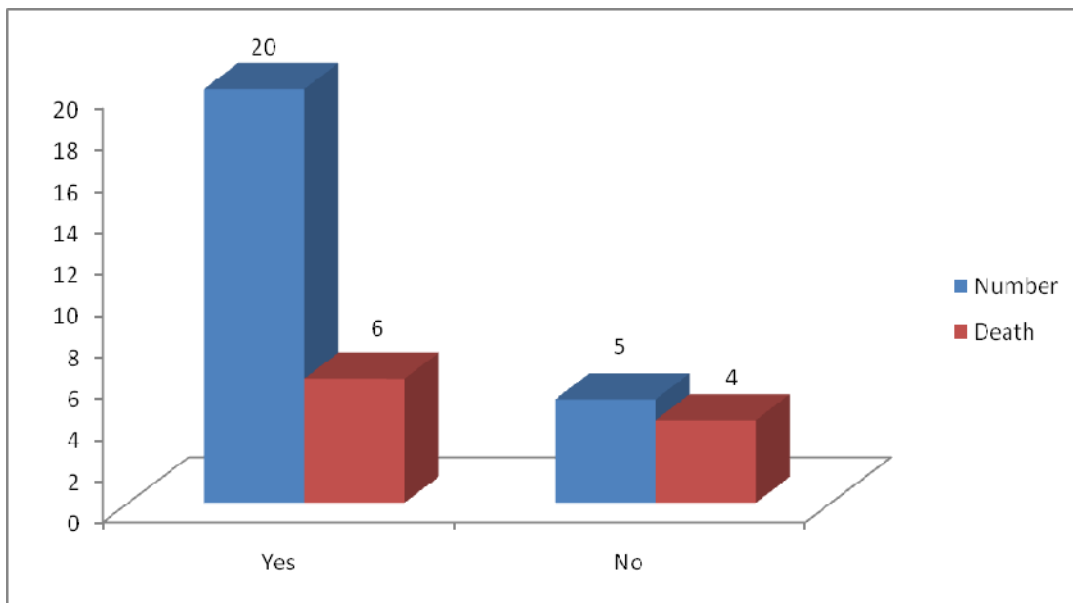
Lymph Node Involvement

	Number	Percentage	Death	Percentage
Not Found	9	36%	-	0%
Node Negative	4	16%	1	25%
Node Positive	12	48%	8	68%



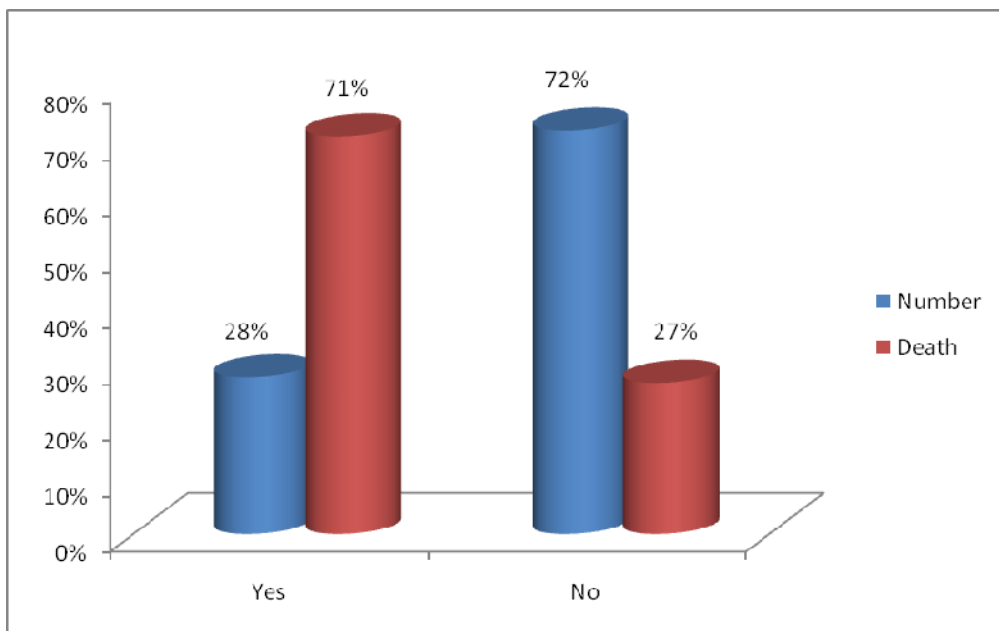
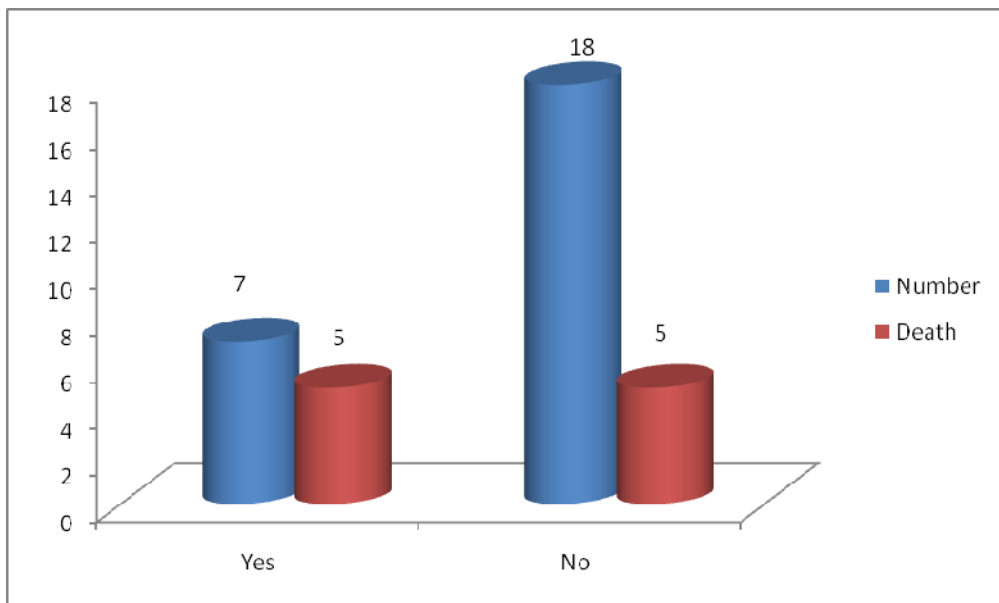
Resectability of the tumour at the time of initial diagnosis:

	Number	Percentage	Death	Percentage
Yes	20	80%	6	30%
No	5	20%	4	80%



Tumour Spillage

	Number	Percentage	Death	Percentage
Yes	7	28%	5	71%
No	18	72%	5	27%



REVIEW OF LITERATURE

Wilms' tumor is the commonest childhood renal tumor and accounts for 6% of all pediatric malignancies ⁽¹⁾. It predominantly affects children less than five years of age, with 90% of new cases diagnosed before age three years. Occasionally, WT has also been described in teenagers and adults.

Wilms' tumor normally develops in otherwise healthy children; however, 10% of cases occur in individuals with recognizable phenotypic syndromes - either overgrowth or non-overgrowth⁽²⁾. The commonest syndromes associated with WT are WAGR syndrome, the Beckwith-Wiedemann syndrome and the Denys-Drash syndrome.

Several epidemiological studies have investigated parental occupational, environmental and lifestyle characteristics as well as birth weight of the child as potential risk factors for Wilms' tumor, but findings to date have been inconsistent and have not been consistently replicated in multiple, high-quality studies in different populations^(3,4). Future epidemiologic studies may benefit from

more detailed exposure assessment, validated by environmental and biologic measurements.

Cytogenetics

Wilms' tumor is predominantly a sporadic disease. Genetic predisposition, however, has been demonstrated in a few patients. Substantial bodies of genetic and molecular studies have contributed important insights into understanding the pathogenesis of WT with several genes being implicated in its etiopathogenesis^(5,6).

The WT gene-1 (WT1) is a tumor suppressor gene located on the short arm of Chromosome 11 (11p13). The normal function of WT1 is required for normal genitourinary development and is important for differentiation of the renal blastema. The identification of this suppressor gene was made on cytogenetic analysis of patients with WAGR syndrome who have more than 30% risk of developing WT. A gene that causes aniridia (PAX-6) is located near the WT1 gene on Chromosome 11p13 and deletions encompassing the WT1 and aniridia genes explain the association between aniridia and WT.

The Denys-Drash syndrome has a 95% chance of WT development and is another syndrome associated with WT1 gene mutation. Although WT1 has a clear role in the tumorigenesis of WT in the above patients, only a small number of patients with sporadic WT have WT1 mutations suggesting that other genes are involved in WT development.

A second WT suppressor gene, WT2, was identified at Chromosome 11p15. Patients with Beckwith-Wiedemann syndrome (BWS) have gene locus in this region and have a 5% risk of developing WT.

In addition to the two genetic loci on Chromosome 11, familial WT predisposition at FWT 1 (17q) and FWT 2 (19q) loci has been identified. Several other genetic loci have been implicated in WT by Loss of heterozygosity (LOH) studies or by the presence of germline translocations, including 16q, 7p, 11q, 22q and loss of 4q.

Clinical Presentation

There are no specific clinical features of WT. Most commonly patients present with a palpable abdominal mass accidentally noted by the parents or in the course of a routine clinical examination. However, about one-third of patients present with abdominal pain, anorexia, vomiting, malaise or a combination of these symptoms. Gross or microscopic hematuria is found in 30% of patients.



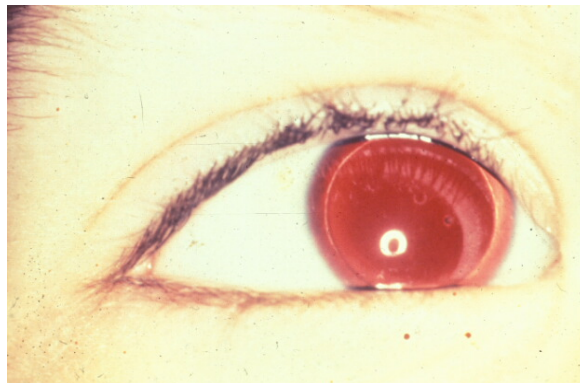
3YR OLD FEMALE CHILD PRESENT AS MASS ABDOMEN

In rare cases of renal vein or caval extension of tumor, varicocele, hepatomegaly, ascites or congestive heart failure may be present. Hypertension is present in about 25% and is attributed to increase in renin activity.

Occasional presentation in a subset of patients is rapid enlargement of the abdomen associated with fever, anemia and hypertension as a result of sudden subcapsular hemorrhage. In rare cases of renal vein or caval extension of tumor, varicocele, hepatomegaly, ascites or congestive heart failure may be present. Acquired von Willebrand's disease may occur in less than 10% of patients.

Associated anomalies and Syndromes present in 15% of patients with Wilms Tumour

ANIRIDIA



HEMIHYPERTROPHY



Denys –Drash syndrome

Male pseudo-hermaphroditism, progressive glomerular disease with Wilms tumour.

Bloom syndrome:

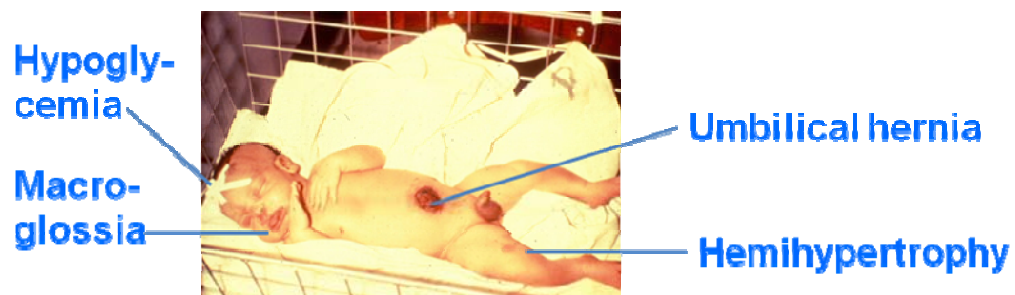
Diminished growth & immunity, facial telangiectasia, trisomy 18, imperforate anus with RUF

WAGR syndrome

Wilms tumour, aniridia, ambiguous genitalia and mental retardation.

Beckwith-Wiedemann syndrome

Macroglossia, gigantism, and umbilical hernia.



IMAGING

Although most patients undergo Ultrasonography (US) as the initial imaging study, the conventional imaging modality for WT has been a computed tomography (CT) scan. It ascertains features of the renal mass, the extent, status and function of the contralateral kidney and intravascular extension of tumor. Real-time ultrasonography can identify the patency and presence of tumor thrombus in the renal vein and the inferior vena cava.

The value of MRI in this disorder is yet to be established, however, a recent study indicated contrast-enhanced CT and T1-W MR images to be of similar potential and superior to US in the diagnosis of nephroblastomatosis and due to the significant radiation dose of serial CT, MR imaging should be the method of choice wherever it is available⁽⁷⁾.

The role of CT scan in the evaluation and subsequent management of pulmonary lesion found only on chest CT scan is controversial and its prognostic importance is equivocal^(8,9). A recent review from National Wilms' Tumor Study (NWTs) 5 of children who had CT-only lung disease demonstrated an inferior outcome for patients treated with vincristine and dactinomycin

(two-drug therapy) only, with or without pulmonary radiation therapy (RT), compared with those who received doxorubicin (DOX) in addition to vincristine and dactinomycin (three-drug therapy)⁽¹⁰⁾.

In addition, there appeared to be no beneficial effect from lung irradiation on the outcome of CT-only patients when chemotherapy was considered. Another study demonstrated CT-only lesions are not invariably tumor, demonstrating the need for histopathological confirmation⁽¹¹⁾.

STAGING

Due to the different treatment schedules adopted by the two large cooperative study groups, two major staging systems are currently used. A forthright, surgery-based system developed by the NWTSG and a delayed surgery-based system developed by SIOP. Although a direct comparison is not practical due to the difference in surgical timing, both staging systems are valuable in predicting outcomes.

NWTS STAGING SYSTEM

Stage I:

The tumor is limited to the kidney and was completely excised. The renal capsule has an intact outer surface.

The tumor was not ruptured or biopsied prior to removal (fine-needle aspiration biopsies are excluded from this restriction).

The vessels of the renal sinus are not involved.

There is no evidence of tumor at or beyond the margins of resection.

Stage II:

The tumor extends beyond the kidney, but was completely excised.

There may be regional extension of tumor (i.e. penetration of the renal capsule or extensive invasion of the renal sinus).

The blood vessels outside the renal parenchyma, including those of the renal sinus, may contain tumor.

The tumor was biopsied (except for fine-needle aspiration), or there was spillage of tumor before or during surgery that is confined to the flank, and does not involve the peritoneal surface.

There must be no evidence of tumor at or beyond the margins of resection.

Stage III:

Residual non-hematogenous tumor is present, and confined to the abdomen.

Any one of the following may occur:

1. Lymph nodes within the abdomen or pelvis are found to be involved by tumor (renal hilar, para-aortic, or beyond). (Lymph node involvement in the thorax, or other extra-abdominal sites would be a criterion for stage IV.)
2. The tumor has penetrated through the peritoneal surface.
3. Tumor implants are found on the peritoneal surface.

4. Gross or microscopic tumor remains postoperatively (e.g. tumor cells are found at the margin of surgical resection on microscopic examination).
5. The tumor is not completely resectable because of local infiltration into vital structures.
6. Tumor spill not confined to the flank occurred either before or during surgery.

Stage IV:

Hematogenous metastases (lung, liver, bone, brain, etc.), or lymph node metastases outside the abdominopelvic region are present.

Stage V:

Bilateral renal involvement is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease prior to biopsy or treatment.

SIOP STAGING SYSTEM

Stage I

- Tumour limited to the kidney or, if outside the normal kidney contour, surrounded with a fibrous pseudocapsule that may be infiltrated with tumor that does not reach the outer surface, and is completely resected.
- Tumor may protrude into the renal pelvis and ureter, but not infiltrate their walls
- Vessels of the renal sinus are uninvolved
- Intrarenal vessels may be involved

Stage II

- Tumor extends beyond kidney or penetrates through renal capsule and / or fibrous pseudocapsule into perirenal fat, but completely resected.
- Tumour infiltrates renal sinus and / or invades blood and lymphatic vessels outside the renal parenchyma, but is completely resected.
- Tumor infiltrates adjacent organs or vena cava but is completely resected.

Stage III

- Incomplete tumor excision that extends beyond resection margins (gross or microscopic tumor remains)
- Tumor penetrates the peritoneal surface
- Tumor implants on peritoneal surface
- Tumor thrombi present at resection margins of vessels or ureter, transected or removed piecemeal by the surgeon
- The tumor has been surgically biopsied before preoperative chemotherapy or surgery

Stage IV

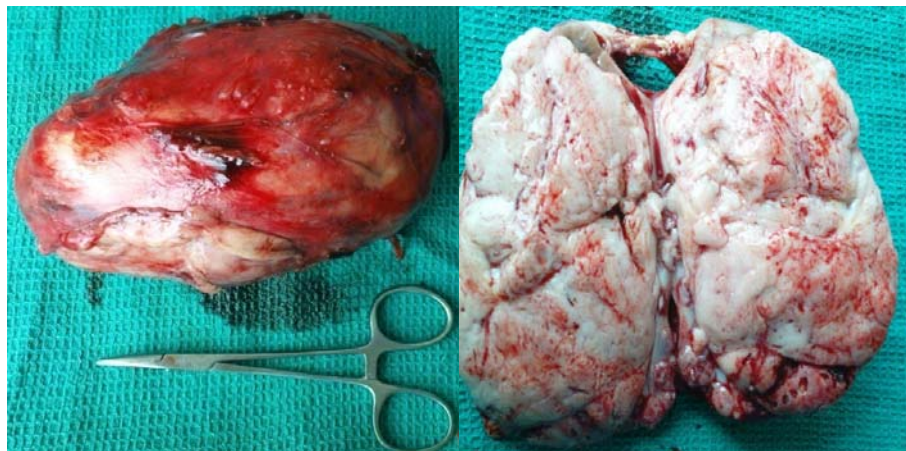
- Hematogenous metastases (lung, liver, bone, brain etc.,) or lymph node metastases outside the abdominal and pelvic region.

Stage V

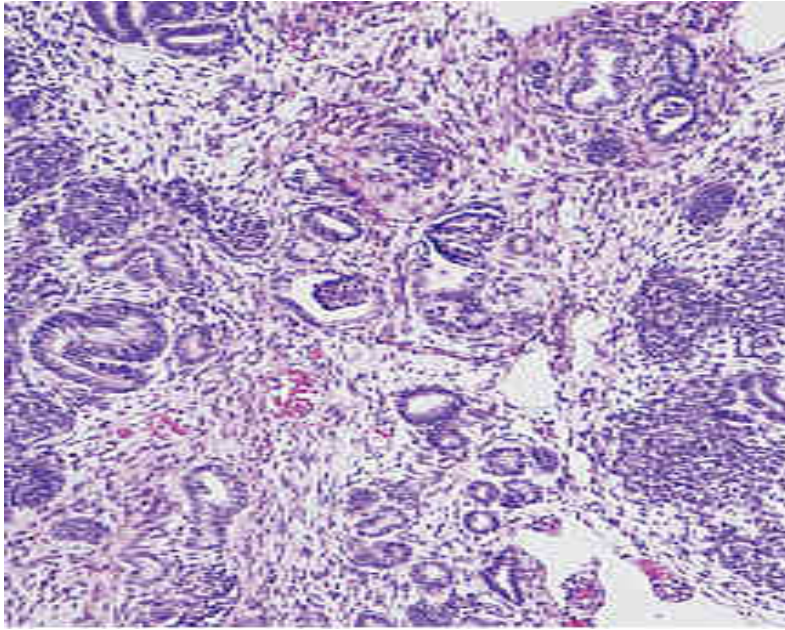
- Bilateral renal tumours present at diagnosis

PATHOLOGY

A classic WT is triphasic, with variable proportions of blastemal, stromal and epithelial components. Some WT are monophasic and have a highly aggressive biological behavior. Histological features in the nephrectomy specimen provide important prognostic information for planning treatment. Presence of nuclear atypia, focal/diffuse anaplasia and sarcomatous elements indicate an unfavorable histology, seen in about 5% of all WT⁽¹²⁾. These account for nearly half of all deaths from this disease. Anaplasia is a marker of resistance to chemotherapy but whether it actually signifies aggressiveness is unknown.



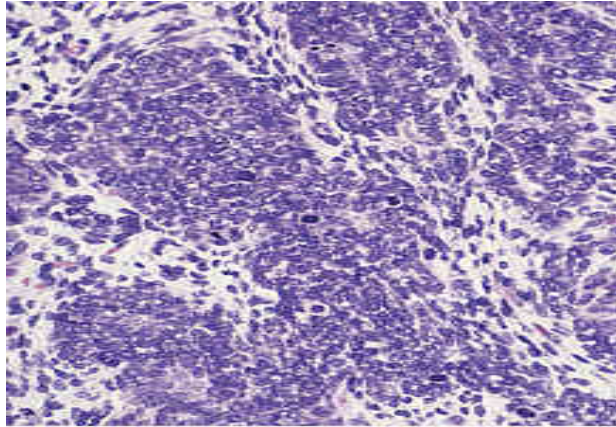
GROSS APPEARANCE OF THE REMOVED SPECIMEN



LOW-POWER MICROSCOPIC VIEW SHOWING A COMBINATION OF BLASTEMA, STROMA, EPITHELIAL TUBULAR FORMATION, AND IMMATURE GLOMERULI.

The SIOP trials recognized three prognostic groups of renal tumors of childhood: low-risk, intermediate-risk and high-risk tumors⁽¹³⁾.

It is important to look for nephrogenic rests in the nephrectomy specimen of WT. A nephrogenic rest is defined as the persistence of metanephric tissues in the kidney after the 36th week of gestation. As they are found in 30-40% of the kidneys removed for WT they may be considered as precursor of WT⁽¹⁴⁾. Nephrogenic rests are subclassified by their position within the renal lobe as perilobar or intralobar.



HIGH-POWER VIEW SHOWING BLASTEMA, STROMA, AND IMMATURE TUBULAR FORMATIONS

The presence of multiple nephrogenic rests is termed as nephroblastomatosis. Only a small number develop clonal transformation into WT while the rest involute spontaneously. The presence of nephrogenic rests within a kidney resected for a Wilms' tumor indicates the need for monitoring the contralateral kidney for tumor development, particularly in young infants⁽¹⁵⁾

Prognostic Factors

The tumor stage at diagnosis, histological features (favorable vs. unfavorable, presence of diffuse anaplasia) and patient age are the most important prognostic determinants which impact on treatment selection and oncological outcome⁽¹⁶⁾. The LOH at chromosome 1p and 16q was prospectively analyzed by NWTs-

5⁽¹⁷⁾. Tumor-specific LOH for both chromosomes was found in approximately 5% of patients with FH WT and was associated with increased risk of relapse and death.

TREATMENT

Wilms' tumor can be considered a model for successful multidisciplinary management of cancer, with improvement in survival from a mere 30% in the 1930s to more than 85% at present. It is also an ideal example wherein the treatment protocols have been devised and modified repeatedly depending on evidence emerging from randomized trials conducted by several cooperative groups and individual institutions.

The most important contributions have been from NWTSG and SIOP, with large numbers of patients enrolled in their studies but with a philosophical difference in their treatment approach. The NWTSG recommends primary surgery before administration of chemotherapy while SIOP advocates administration of four weeks of chemotherapy prior to surgery.

The former approach allows accurate documentation of histology and tumor extent prior to chemotherapy and also enables

the collection of untreated tumor for biology studies and provides an unadulterated view of the tumor's molecular biology. The latter approach downstages the disease, makes surgery easier and reduces the chances of spillage with consequent reduction in abdominal and distant relapse but carries a risk of non-WT histology being present in the primary tumor. Besides, histologic response to chemotherapy can be assessed postoperatively which provides valuable prognostic information⁽¹²⁾.

The NWTSG advocates preoperative chemotherapy only in the presence of WT in a solitary or horseshoe kidney, bilateral tumors, venal caval thrombus above hepatic veins or severely symptomatic lung metastases⁽¹⁸⁾. Since both these approaches have yielded excellent results, there is still a debate concerning the preferred approach, but individualization of treatment based on tumor size and extent, general condition of the patient and surgeon's experience would probably be needed for best outcome.

Surgery

The timing of surgery with regards to preoperative therapy has varied between the European and the North American group. Nevertheless surgical resection is an important constituent in the

multimodal management of WT. Radical nephrectomy is the standard of care for these patients with resectable tumors. A transperitoneal route is preferred to provide adequate exposure for complete staging, which includes inspection for local tumor extension, hilar and regional lymph nodes, liver metastases and peritoneal seedlings.

Debates about the exploration of the contralateral kidney at surgery exist but evidence now suggests it can be omitted. Data from the NWTs 4 study showed that omission of routine exploration does not affect the outcome or management of newly diagnosed WT, if adequate preoperative CT or MRI is obtained⁽¹⁹⁾. Prevention of tumor spillage should be of prime concern as this has a bearing in upstaging the tumor, hence gentle handling and careful removal is mandatory⁽²⁰⁾.

The IVC and the renal vein should be palpated for the presence of tumor thrombus, which if present (renal vein thrombus seen in about 6% patients) should be removed en bloc with the kidney⁽²¹⁾. Generally, WT does not infiltrate the adjoining structures, hence a radical en bloc resection is rarely needed,

however, a wedge resection if can be performed safely may help in down-staging the tumor to Stage II.

As regards lymph node dissection, sampling of suspicious lymph node is recommended instead of a formal lymph node dissection. An adequate and careful surgical resection is mandatory for optimal treatment outcome since incomplete resection, tumor spillage and omission of lymph node sampling are all reported to be associated with abdominal recurrence. Although surgical complications have significantly reduced, surgical morbidity should not be overlooked. Indeed surgical specialists who primarily treat children can perform these operations with lower surgical morbidity⁽²⁰⁾. Tumor spillage and intraperitoneal dissemination increases the risk of intra abdominal relapse but the current data suggests that overall survival is not adversely affected⁽²⁰⁾.

Partial nephrectomy in the routine management of WT has not gained popularity. The reasons being most WT are large or centrally located making only less than 5% eligible for partial nephrectomy at presentation and even after preoperative chemotherapy only about 10% would be feasible for a nephron-

sparing surgery^(22,23). These surgeries carry a risk of leaving behind nephrogenic rest in addition to other procedure-related complications. Besides, the rate of renal failure in patients with unilateral WT is less than 1%⁽²⁴⁾.

Hence partial nephrectomy is only recommended for patients with synchronous or metachronous bilateral tumors, tumors in solitary kidneys, renal insufficiency of any etiology and children with risk of multiple neoplasms such as in BWS. Laparoscopic nephrectomy with lymph node sampling has been described in the literature but long-term experience is lacking⁽²⁵⁾.

CHEMOTHERAPY

Chemotherapy plays a very important role in the management of WT. The current first line drugs for WT are vincristine, dactinomycin and doxorubicin. The second line drugs for non-responsive or relapsed disease are ifosphamide, etoposide, carboplatin and cyclophosphamide. Large cooperative groups have different chronology for deliverance of chemotherapy, drug combination and duration, which have been refined over successive trials to optimize survival rates while minimizing acute

and long-term toxicities. It is indeed noteworthy that despite these differences, the survival results amongst all groups are similar.

The SIOP and UKCCSG group has favored the use of preoperative chemotherapy in an attempt to down-stage the tumor, whereas the NWTSG advocates upfront nephrectomy without preoperative therapy in order to precisely identify the tumor stage.

Radiotherapy

As a result of the NWTSG and SIOP studies the role of surgery has been customized though not eliminated. Radiation was an important treatment modality in preoperative and adjuvant settings in the earlier studies. With subsequent refinement in therapy with an aim of maximizing cure and reducing morbidity, there are now precise indications for adjuvant radiotherapy. The current standard of care includes flank/abdominal irradiation (10·8Gy in six fractions) for Stage III favorable-histology (FH) tumors and Stage II-III diffuse anaplastic WT⁽¹⁾.

The role of lung irradiation in metastatic disease is unresolved with difference among the groups. The NWTSG continues to administer whole lung irradiation (12Gy in eight

fractions) in patients with pulmonary metastases, while the SIOP group advocates omission of radiotherapy for patients whose lung metastases disappear completely after six weeks of pre-nephrectomy chemotherapy with vincristine, dactinomycin and doxorubicin.

The role of pulmonary irradiation in children with pulmonary metastases visible on CT but not chest radiograph is further mystified. Use of conformal radiotherapy as well as IMRT has led to dose escalation without increase in morbidity. Similarly, use of high-dose intraoperative radiation therapy for WT has been reported.⁽²⁾

TUMOR STAGE AND TREATMENT

The histologic grade and stage of the tumor are the most important determinants of outcome in Wilms' tumor. An accurate intraoperative staging is required to assess the requirements for postoperative treatment with chemotherapy or radiotherapy.

Stage I FH

Stage I WT FH has an excellent prognosis. The NWTSG recommends primary surgery followed by adjuvant two-drug

chemotherapy (vincristine and pulse intensive dactinomycin) for 18 weeks based on NWTSG 1-3 trials^(26,27,28), whereas the SIOP approach uses the same drugs either side of surgery for a total of eight weeks based on several SIOP studies.^(29, 30) Radiation therapy is not necessary in these patients if they receive adjuvant chemotherapy, as demonstrated by the initial three NWTSG trials^(26,27,28) as well as the SIOP 5 trial.⁽³¹⁾

Surgery without chemotherapy was evaluated in NWTSG-5 in a select group of patients with highly favorable features (infants younger than 24 months and whose nephrectomy specimen weighed less than 550g⁽³²⁾). The study was designed with a stringent stopping rule (interim analysis of RFS $\leq 90\%$) and reported 13.5% relapse rate at two years, mandating the closure of the study. Most patients could be successfully salvaged with chemotherapy, however, with a two-year overall survival (OS) rate of 100%. In the light of this, further studies are re-evaluating the role of nephrectomy alone in this highly selected group of patients.

The NWTSG-3⁽²⁸⁾ reported 92.5% RFS and 97.6% OS at 16 years and NWTSG-5⁽³³⁾ reported 92.4% RFS and 98.3% OS at four years for these patients. Similarly the SIOP 93-01⁽³⁴⁾ has reported

a five-year RFS rate of 88.3% and five-year OS rate of 97% in these patients. The UKWG 2-3 reported 86.5% EFS and 94.7% OS at four years^(35,36).

Stage II

Currently, the NWT5-5^(32,33) recommends primary surgery followed by 18 weeks of chemotherapy with vincristine and pulse-intensive dactinomycin. Addition of postoperative radiotherapy (RT) or doxorubicin was not shown to impart survival benefit in the NWT5-3.⁽³⁰⁾ The SIOP 93-01 trial⁽³⁴⁾ recommends preoperative four weeks of chemotherapy with vincristine and pulse-intensive dactinomycin and addition of doxorubicin in postoperative chemotherapy for 27 weeks. Node-negative patients do not receive postoperative RT provided they receive postoperative epirubicin (SIOP-9)⁽³⁰⁾ while node-positive receive 15Gy RT to the tumor bed in addition to three-drug chemotherapy.

The NWT5 -3 reported 89.6% RFS and 92.9% OS at 16 years and the NWT5- 4⁽³⁷⁾ trial 83.6% RFS and 93.8% OS at eight years for Stage II FH WT. The SIOP-9 reported 85% RFS and 88% OS at two years in node-negative stage patients.

Stage III

The NWTs-5 recommends surgery followed by abdominal radiation (10.8Gy) and 24 weeks of chemotherapy with vincristine, doxorubicin and pulse-intensive dactinomycin. The SIOP 93-01 trial recommends preoperative four weeks of chemotherapy with vincristine and pulse-intensive dactinomycin and 27 weeks of three-drug chemotherapy with vincristine, doxorubicin and dactinomycin in addition to postoperative 15Gy abdominal radiotherapy.

The results of the NWTs-3 trial showed that the addition of doxorubicin to chemotherapy resulted in reduction of radiation dose from 20Gy to 10Gy for Stage III/FH patients. The NWTs-4 trial reported six months chemotherapy to be sufficient for Stage III/FH patients.

The NWTs-3 has reported 80.4% RFS and 86.2% OS at 16 years and NWTs- 4 reported 88.9% RFS and 93% OS at eight years for Stage III FH patients. The SIOP-9 reported 71% RFS and 85% OS at two years in patients with Stage III and Stage II node-positive FH patients.

Stage IV

The NWTSG recommends nephrectomy with lymph node sampling, abdominal radiation 10.8Gy according to local stage of renal tumor (i.e. for Stage III), and bilateral pulmonary radiation 12Gy for patients with chest X-ray evidence of pulmonary metastases and 24 weeks of chemotherapy with vincristine, doxorubicin and pulse-intensive dactinomycin. The NWTSG-3 reported 76.5% RFS and 79.5% OS at 16 years and NWTSG-4 reported two-year RFS of 80.6% and OS of 89.5% for Stage IV FH patients.

The SIOP advocates six weeks of preoperative chemotherapy with vincristine, dactinomycin and doxorubicin followed by surgery. Those who attain CR by Week 9 receive 27 weeks of three-drug chemotherapy as the preoperative one without radiation therapy. Those whose pulmonary metastases do not respond completely to chemotherapy, with or without surgical excision of residual metastases by Week 9 are advised postoperative 12Gy whole-lung irradiation and four-drug chemotherapy (ifosfamide, carboplatin, etoposide and doxorubicin) for 37 weeks. This helps in limiting the number of children who are exposed to whole-lung radiation, with its inherent associated toxicity.⁽³⁸⁾ The SIOP reported 83% four year RFS.

Management of Anaplastic Tumors

Stage I:

Focal or diffuse anaplastic tumors: The NWTSG-5 trial has reported 69.5% RFS and 82.6% OS at four years for Stage I focal or diffuse anaplastic histology patients, using surgery followed by 18 weeks of chemotherapy with vincristine and pulse-intensive dactinomycin. However, due to these suboptimal results, the future studies plan to include abdominal radiation and doxorubicin into the treatment regimen of these patients. The SIOP approach uses the same drugs either side of nephrectomy for a total of eight weeks.

Stages II-IV:

For patients with Stage II-IV WT with focal anaplasia, NWTSG-5 advocates primary surgery followed by abdominal radiation and adjuvant three-drug chemotherapy with vincristine, doxorubicin and dactinomycin. For those with diffuse anaplasia, patients are advised postoperative abdominal radiation and adjuvant chemotherapy regimen consisting of vincristine, doxorubicin and cyclophosphamide alternating with cyclophosphamide and etoposide. This change of chemotherapy was warranted due to the results of NWTSG-4 which showed that the four-year RFS was considerably improved (27% to 55%) with the addition of cyclophosphamide.

The NWTs- 5 reported four-year RFS of 55.1% and 74.9% for patients with diffuse and focal anaplasia respectively. Four-year RFS estimates for Stage II, III, IV were 82.1%, 68.3% and 37.5% respectively.

Stage V

Synchronous bilateral WT account for 6% of all WT and also pose a special challenge⁽¹⁾. The goal of therapy for patients with bilateral disease, beyond cure of the tumor, is to spare renal parenchyma to avoid significant renal insufficiency and hence the treatment must be individualized.

The NWTs-2 and 3 studies have demonstrated no difference in survival for children who undergo initial bilateral biopsy followed by chemotherapy and then surgical resection compared with patients who have initial resection followed by chemotherapy⁽³⁹⁾. However, preoperative chemotherapy often results in significant reduction in tumor size, thereby facilitating subsequent renal salvage. The NWTs-4 reported only 8.2% risk of local relapse following nephron-sparing surgery⁽⁴⁰⁾.

The NWTs-5 recommendations for the management of bilateral WT include initial biopsy and local staging followed by chemotherapy (according to abdominal stage and histologic features) and second-look surgery at Week five⁽¹²⁾. Additional radiation and chemotherapy maybe given if indicated but the surgery must be completed by 12 weeks from diagnosis to prevent development of drug-resistant clones.

Initial treatment is with vincristine and dactinomycin if the renal tumors are of favorable histology and not more extensive than Stage II. Those with higher stage and favorable histology disease should receive doxorubicin, vincristine and dactinomycin and those with anaplastic histology should receive cyclophosphamide in addition to vincristine, doxorubicin and etoposide. Following six weeks of chemotherapy, the patient should be reassessed. If serial imaging studies show no further reduction in tumor, a second-look surgical procedure should be performed (partial nephrectomy on one side if possible) if negative margins can be obtained; otherwise, another biopsy should be done to confirm viable tumor⁽⁴¹⁾.

Chemotherapy and/or radiation therapy following the second-look operation is dependent on the response to initial therapy, with more aggressive therapy required for patients with inadequate response to initial therapy observed at the second procedure. Radical nephrectomy is recommended when nephron-sparing surgery is not possible. Approximately 10% of patients with bilateral tumors have anaplastic histology and may benefit from more aggressive chemotherapy and radiation therapy and an aggressive surgical approach at the second-look operation.

Renal transplantation for children with WT is usually delayed until one to two years have passed without evidence of malignancy⁽⁴²⁾.

Experience from an Indian Center

Bhagwat *et al.* (2005) reported their experience from a major oncology tertiary care referral center in India⁽⁴³⁾. At their center, Wilms' tumor constitutes 3.5% of approximately 800 new pediatric cancers registered every year and is the most common solid tumor after brain tumors and neuroblastoma.

In the earlier years, many of their patients were referred to their institute after primary surgery performed elsewhere, leading to a considerable delay in starting adjuvant treatment. However, in recent times, the majority of patients were operated per primum at their center. Whenever surgery was done outside, every effort was made to stage the disease based on the referring clinician's preoperative and intraoperative examination findings and imaging studies. All patients were evaluated in a multidisciplinary Pediatric Oncology tumor board and treated as per the standard institutional protocol which included three-drug chemotherapy (vincristine, dactinomycin and doxorubicin) for all the patients as given for advanced stages in the NWTS-4 to compensate for lacunae in staging.

The overall survival and relapse-free survival of 118 WT patients treated over a 10-year period were 77.6% and 73.4% at 10 years respectively. The overall survivals for Stages I-IV were 83%, 81%, 47% and 75% respectively. These results need to be seen in light of the fact that many patients during this period underwent surgery at an outside center, with incomplete staging, inadequate surgery or tumor spillage during surgery.

RECURRENT WT

The prognosis of recurrent WT used to be dismal, with the majority of patients receiving the same treatment at salvage as their primary treatment and with survival rates of less than 30% despite standard therapy by current standards (judicious surgery, chemotherapy with or without radiation therapy). However, in recent times, drugs like platinum compounds, ifosphamide, cyclophosphamide, etoposide etc and their combinations have shown considerable activity in patients with relapsed WT. Post-relapse survival rates of 50-60% have been reported with ifosphamide, etoposide and carboplatin (ICE) chemotherapy⁽⁴⁴⁾.

Factors which predict better survival are relapse-free interval of more than 12 months, low stage of primary disease, low metastatic burden, two-drug chemotherapy and no previous radiation to tumor bed⁽⁴⁵⁾. Complete resection of the recurrent lesion(s) has also been shown to be a favorable prognostic factor but whether it reflects only low-volume recurrent disease rather than actual survival benefit is yet debatable⁽⁴⁴⁾. High-dose chemotherapy with autologous stem cell rescue is being tried in clinical trials but is presently experimental⁽⁴⁶⁾.

Novel drugs and strategies are needed to improve clinical outcome in this group of patients. Metachronous tumors in the contralateral kidney account for 2% of WT, with children younger than 12 months with perilobar nephrogenic rests at a higher risk⁽⁴⁷⁾. The contralateral tumors need to be treated independently as the tumors in the first kidney. Although patients with metachronous tumors have a worse survival than those with synchronous tumors (five and 10-year OS of 49.1% and 47.2%); in the former group, those developing after 18 months of initial diagnosis fare better than those developing earlier (10 year OS 55.2% vs. 39.6%)⁽⁴⁹⁾.

Long-Term Sequele

With long-term follow-up data being available in a large number of survivors of WT, the long-term sequele of treatment are becoming better defined. Renal failure after surgical management of unilateral WT is rare. Cardiac problems secondary to anthracycline administration compounded by whole-lung radiotherapy as well as pulmonary complications secondary to whole-lung radiotherapy are real concerns and need to be addressed⁽⁴⁹⁾. Gonadal dysfunction secondary to chemo and/or radiotherapy may occur. Children treated for WT are also at an increased risk of second malignancy, especially if they have also received radiotherapy in addition to chemotherapy⁽¹⁾.

DISCUSSION

The development of effective systemic chemotherapy in the 1960s rapidly changed the outcome and approach to treatment of Wilms' tumor. Randomized clinical trials have been conducted by NWTSG, SIOP, and the United Kingdom Children's Cancer Study Group (UKCCSG) to determine the appropriate role for each of the therapeutic modalities available. Patients are stratified into different treatment groups based on extent of disease and histopathologic features. The goals of these trials are to allow a reduction in the intensity of therapy for most patients, while maintaining overall survival, and to decrease potential late sequelae.

After instituting the various recent modalities of treatment in Wilms tumour, the overall survival rate significantly increased from 20% in 1920 to 90 % in 2000 as per recent NWTSG reports.

In our study the overall survival rate is 60% (15 out of 25 children).

In another report from our country (Bhagawat et al.)⁴³ shows 83% overall survival rate in a large cohort of patients. Marilia Fornaciari et al.. from Brazil report 84.6% overall survival rate in 132 patients.

Most of our cases present lately and majority of the cases were in advanced stages (14 of 25 were stage 3 and stage 4), which may be the possible cause for lower survival rates.

Another possible explanation is – loss of Hetrozycocity(LOH) i.e., chromosomal loss in 1p and 16q may be the caused for poor prognostic outcome.

Five children with stage I tumour and three children with stage II tumours have survived more than 5 years. This is comparable with recents NWTSG and SIOP trials.

Gender:

Out of the 25 children 13 were female and 12 were male. Male female ratio is almost equal and the mortality rate is also comparable with both groups(41% Males and 38% Females). So gender has no prognostic significance in our study.

Age Group:

More number of deaths(60%) have occurred in less than 23 months age group(3 out of 5 cases), but in the Brazilian study and recent NWTSG reports prognosis is good in this age group(10% mortality in Brazilian Study⁽⁵⁰⁾). Again advanced stages and unfavourable histology in 2 children maybe the possible explanation for higher mortality.

Mortality in later age group 24 to 47 months and more than 48 months is 33% and 37% respectively. This is comparable with Brazilian study.

Tumour staging is one of the main prognostic indicator that determines the outcome of treatment and survival in Wilms tumour. The survival rate based on staging is comparable to other studies except in Stage III tumours.

	Our Study	Brazilian Study (1999 - 2000)	NWTSG Reports (2005)	UKCCSG (2000)
STAGE I	100%	100%	96%	94%
STAGE II	80%	94.2%	86%	91%
STAGE III	38%	51%	81%	84%
STAGE IV	25%	31.3%	75%	70%
STAGE V	50%	--	--	--

Even though it is difficult to explain, the higher mortality rate in our group compared to NWTS results, irregular follow-up for the treatment, and toxicity to chemotherapy may be possible explanations for this. So early cases in Stage I and Stage II tumours response well to treatment and prognosis good.

Children with favourable histology (Triphasic pattern and no anaplasia) has good prognostic outcome. Only 3 deaths occurred out of 17 cases in our group as comparable to higher mortality rate (87%) in unfavourable histology group. (Focal or diffuse anaplasia).

This observation with comparable with Brazelian study. But NWTS reports the mortality rate in unfavourable histology group is 40%.

In our series, 5 patients had received pre-operative chemotherapy. Of this 5 cases, only 1 patient had remnant of blastimal elements in final pathology report. That patient expired.

In 2002, SIOP trials noted that certain histology features that remain after pre-operative chemotherapy, such as blastema or prognostic significance whereas others not.

Therefore in the further SIOP trials, a revised classification of renal tumours to be followed for the treatment purposes.

- Completely necrotic (low risk group)
- Blastemic (high risk group)
- Others (Intermediate group)

Resectability of the tumour completely at the time of initial surgery has significance prognostic value in our observation. Among the 25 cases, 20 cases were completely resectable, and mortality rate in this group, only 30% has comparable to 80% mortality rate when the tumour is inoperable.

Early mortality in Wilms tumour occur in 7 of our cases. Tumour bed recurrence occur in 2 of our cases. Out of the 9 cases, tumour spillage occur in 7 cases and surgical margin positivity in 3 cases.

Tumour spillage and surgical margin positivity were the attributed cause for early mortality, and tumour bed recurrence in our observation.

As per recent NWTS report 10% of patients has poor prognostic variable including

- Unfavourable histology
- Chromosome loss in 1p and 16q (loss of Heterozygosity)
- Diploidy

However, gene mapping facilities are not available in our hospital, the prognostic significance of these factors are not able to study.

IVC Extension:

Tumour thrombus in IVC found in 3 of our patients, in all patients tumour thrombus was removed enblock. All 3 patients were survived. So the tumour thrombus involvement below the hepatic veins has not affect the survival of the patients.

Syndromic Association:

In our series, only 1 patient had aniridia and nystagmus this patient is surviving more than 5 years. Otherwise, none of our patients had any syndromic association.

Tumour in Horse Shoe Kidney:

One patient in Wilms tumour in horse shoe kidney. The tumour was confined to one pole of the kidney (Stage I). This patient was treated with nephrectomy and chemotherapy. He is surviving for more than 3 years.

Bilateral tumours:

Two of our patients had bilateral tumours. One patient had Stage III on right side and Stage II on left side. This patient was treated with right nephrectomy followed by chemotherapy and radiotherapy who has expired after 6 months. In another patient both side Staged tumour treated with chemotherapy and radiotherapy, surviving more than 3 years. 2 patients had recurrent Wilms tumour treated with salvage chemotherapy (ICE Regimen – Ifosfamide, Cisplatin, Etoposide).

One patient had liver metastasis after completion of the chemotherapy who was also treated with salvage chemotherapy. She survives more than 2 years with secondaries.

To summarize our experience, tumour staging and histopathology are the two main prognostic indicator that determines the survival of Wilms tumour.

Higher mortality rate was found in less than 24 months age group and older children.

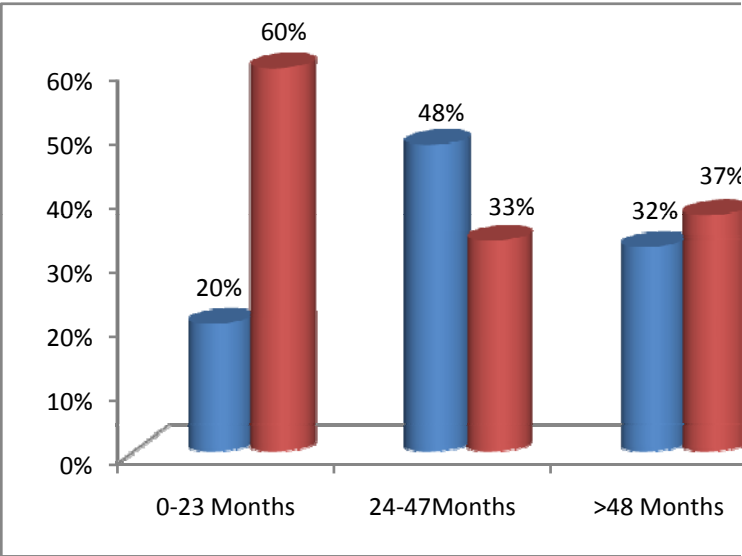
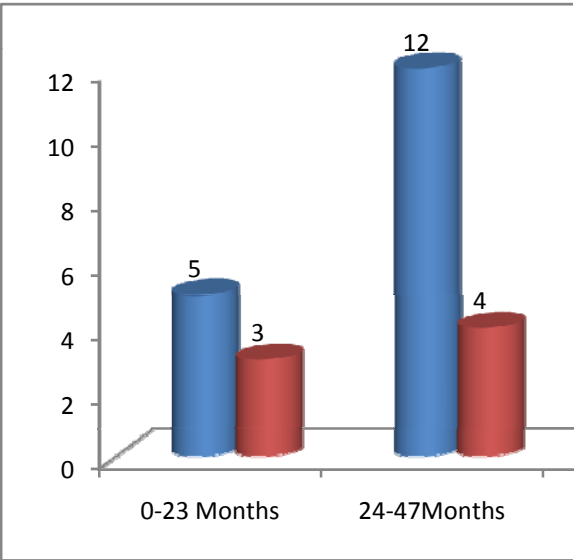
Resectability of the tumour at the time of initial diagnosis has significance prognostic value. Tumours spillage and lymph nodal involvement are the causes of early mortality and Wilms tumour.

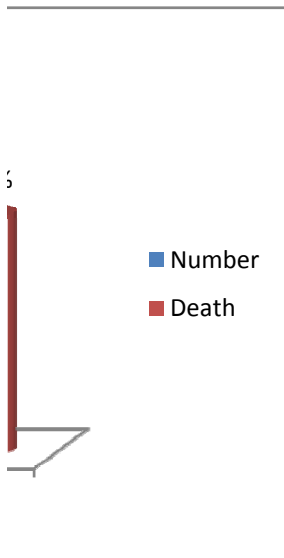
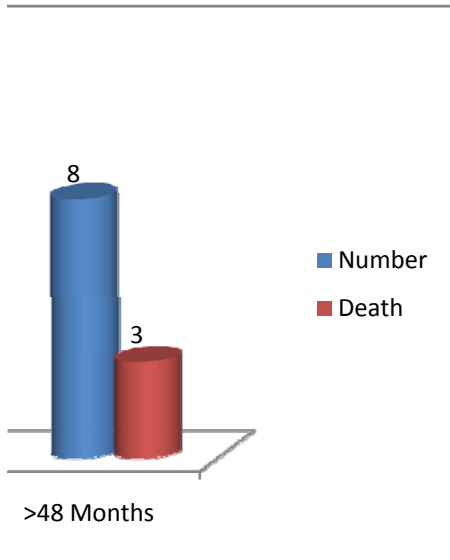
CONCLUSION

- Stage I tumours had 100% survival rate.
- The mortality rate was higher in Stage III and Stage IV tumours (more than 75%).
- The unfavourable histology group had 80% mortality rate.
- Higher mortality rate was observed in less than 24 months age group.
- Resectability of the tumour at the time of initial diagnosis has significant prognostic value.
- Tumours spillage and lymph nodal involvement are associated with early mortality and recurrent tumour.
- Considering the constraints of the size of the study, it needs further follow-up to assess the long term prognostic variables.

	Number	Death
0-23 Months	5	3
24-47Months	12	4
>48 Months	8	3

	Number	Death	
0-23 Months	20%	60%	
24-47Months	48%	33%	
>48 Months	32%	37%	





S.No.	Name	Age	Sex	Side	Stage	Pathology	Tumour Spillage	LN	Survival
1.	Priya	3½	F	Left	Stage III	Triphasic -no anaplasia	++(intraabdominal)	+	6 months
2.	Gowri	9½	F	Left	Stage II	Triphasic -no anaplasia	++	-	3 months
3.	Sasidharan	7½	M	Left	Stage II	Monophasic-no anaplasia	-	+	Survived
4.	Kanagaraj	8	M	Left	Stage III	Triphasic -no anaplasia	++	+	Expired after 4 months
5.	Sangameswaran	3	M	Right	Stage III	Triphasic -no anaplasia	++	+	Expired after 1 year
6.	Yasodha	1½	F	Left	Stage I	Biphasic anaplasia+	-	-	Survived - 5 years
7.	Niketha	1½	F	Right	Stage III	Difuse Anaplasia	-	+	Expired after 3 months
8.	Gowtham	2½	M	Right	Stage II	Triphasic -no anaplasia	-	+	Survived
9.	Nivetha	3½	F	Left	Stage IV	Monophasic -anaplasia+	-	+	Expired after 5 months
10.	Prasanth	2	M	Right	Stage I	Triphasic -no anaplasia	-	-	Survived
11.	Boopathy	4	M	Left	Stage IV	Triphasic -difuse anaplasia	-	-	Expired after 2 months
12.	Aravindh Kumar	3	M	Left	Stage III	Difuse Anaplasia	-	+	Survived
13.	Tamilarasan	1½	M	Right	Stage I	Triphasic - no anaplasia	-	-	Expired after 3 months
14.	Bharath Kumar	11	M	Right	Stage IV	Anaplasia+	-	-	Expired after 6 months
15.	Priya	8	F	Right	Stage III	Anaplasia+	+	+	Survived
16.	Ajith	9	M	Left	Stage I	Triphasic -no anaplasia	-	-	Survived
17.	Gayathri	9	F	Right	Stage IV	Triphasic -no anaplasia	+	+	Expired after 1 year
18.	Sudha	7	F	B/L	[R] Stage III [L] Stage I	Triphasic -no anaplasia	+	+	Expired after 1 year
19.	Boopathi	10	F	Right	Stage II	Difuse Anaplasia	+	+	Expired after 4 months
20.	Keerthana	4	F	Left	Stage III	Triphasic -no anaplasia	-	-	Survived with secondaries
21.	Prem Kumar	3	M	Left	Stage III	Triphasic -no anaplasia	-	+	Survived - 1 ½
22.	Kavya	7	F	Left	Stage III	Triphasic -no anaplasia	+	+	Survived with secondaries
23.	Rabia	3	F	Left	Stage I	Triphasic -no anaplasia	+	+	Survived
24.	Md. Asik	4	M	Left	Stage I	Triphasic -no anaplasia	-	-	Survived
25.	Suba	3	F	B/L	[R]Stage II [L]Stage I	Triphasic -no anaplasia	+	+	Survived

PROFORMA

Name :

IP no:

Age/Sex :

Ca No:

Address :

PS No:

Date of Surgery:

Date of discharge:

Phone No:

Diagnosis with Staging:

Clinical presentation:

Duration of symptoms

- Pain
- Mass
- Haematuria
- Loss of weight
- Loss of appetite
- Other symptoms

Investigations

- Hb
- Urine routine
- Urea
- S.Creatinine
- USG Abdomen
- CT Abdomen

- IVP
- Urea
- S.Creatinine

Biopsy Report:

Surgery Details:

DOS	Size of Tumor	LN	Opp.Kindey	Renal Vein	Complications

Post of follow up:

Radiotherapy:

Chemotherapy: Schedule

Period of follow up:

Secondaires

Disease free survival

Reference

If death details

Repeat and follow up investigations

USG Abdomen

CT Abdomen

Final Outcome

BIBLIOGRAPHY

1. Kalapurakal JA, Dome JS, Perlman EJ, Malogolowkin M, Haase GM, Grundy P, *et al* . Management of Wilms' tumour: Current practice and future goals. *Lancet Oncol* 2004;5:37-46.
2. Gommersall LM, Arya M, Mushtaq I, Duffy P. Current challenges in Wilms' tumor management. *Nat Clin Pract Oncol* 2005;2:298-304.
3. Sharpe CR, Franco EL. Etiology of Wilms' tumor. *Epidemiol Rev* 1995;17:415-32.
4. Breslow N, Olshan A, Beckwith JB, Green DM. Epidemiology of Wilms tumor. *Med Pediatr Oncol* 1993;21:172-81.
5. Tay JS. Molecular genetics of Wilms' tumour. *J Paediatr Child Health* 1995;31:379-83.
6. Slater RM, Mannens MM. Cytogenetics and molecular genetics of Wilms' tumor of childhood. *Cancer Genet Cytogenet* 1992;61:111-21.
7. Rohrschneider WK, Weirich A, Rieden K, Darge K, Troger J, Graf N. US, CT and MR imaging characteristics of nephroblastomatosis. *Pediatr Radiol* 1998;28:435-43.

8. Green DM. Use of chest computed tomography for staging and treatment of Wilms' tumor in children. *J Clin Oncol* 2002;20:2763-4.
9. Owens CM, Veys PA, Pritchard J, Levitt G, Imeson J, Dicks-Mireaux C. Role of chest computed tomography at diagnosis in the management of Wilms' tumor: A study by the United Kingdom Children's Cancer Study Group. *J Clin Oncol* 2002;20:2768-73.
10. Dirks A, Li S, Breslow N, Grundy P. Outcome of patients with lung metastases on NWTs 4 and 5. *Med Pediatr Oncol* 2003;41:251-2.
11. Ehrlich PF, Hamilton TE, Grundy P, Ritchey M, Haase G, Shamberger RC, *et al* . The value of surgery in directing therapy for patients with Wilms' tumor with pulmonary disease. A report from the National Wilms' Tumor Study Group (National Wilms' Tumor Study 5). *J Pediatr Surg* 2006;41:162-7.
12. Metzger ML, Dome JS. Current therapy for Wilms' tumor. *Oncologist* 2005;10:815-26.
13. Vujanic GM, Sandstedt B, Harms D, Kelsey A, Leuschner I, de Kraker J, *et al* . Revised International Society of Paediatric Oncology (SIOP) working classification of renal tumors of

childhood. Med Pediatr Oncol 2002;38:79-82.

14. Beckwith JB. Nephrogenic rests and the pathogenesis of Wilms tumor: Developmental and clinical considerations. Am J Med Genet 1998;79:268-73.
15. Beckwith JB. Wilms' tumor and other renal tumors of childhood: A selective review from the National Wilms' Tumor Study Pathology Center. Hum Pathol 1983;14:481-92.
16. Breslow N, Sharples K, Beckwith JB, Takashima J, Kelalis PP, Green DM, *et al* . Prognostic factors in nonmetastatic, favorable histology Wilms' tumor: Results of the Third National Wilms' Tumor Study. Cancer 1991;68:2345-53.
17. Grundy PE, Breslow NE, Li S, Perlman E, Beckwith JB, Ritchey ML, *et al* . Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: A report from the National Wilms Tumor Study Group. J Clin Oncol 2005;23:7312-21.
18. Shamberger RC. Pediatric renal tumors. Semin Surg Oncol 1999;16:105-20.
19. Ritchey ML, Shamberger RC, Hamilton T, Haase G, Argani P, Peterson S. Fate of bilateral renal lesions missed on preoperative imaging: A report from the National Wilms Tumor

Study Group. J Urol 2005;174:1519-21.

20. Shamberger RC, Guthrie KA, Ritchey ML, Haase GM, Takashima J, Beckwith JB, *et al* . Surgery-related factors and local recurrence of Wilms tumor in National Wilms Tumor Study 4. Ann Surg 1999;229:292-7.
21. Shamberger RC, Ritchey ML, Haase GM, Bergemann TL, Loechelt-Yoshioka T, Breslow NE, *et al* . Intravascular extension of Wilms tumor. Ann Surg 2001;234:116-21. <#>
22. Wilimas JA, Magill L, Parham DM, Kumar M, Douglass EC. The potential for renal salvage in non metastatic unilateral Wilms' tumor. Am J Pediatr Hematol Oncol 1991;13:342-4.
23. Moorman-Voestermans CG, Aronson DC, Staalman CR, Delemarre JF, J de Kraker. Is partial nephrectomy appropriate treatment for unilateral Wilms' tumor? J Pediatr Surg 1998;33:165-70.
24. Ritchey ML, Green DM, Thomas PR, Smith GR, Haase G, Shochat S, *et al* . Renal failure in Wilms' tumor patients: A report from the National Wilms' Tumor Study Group. Med Pediatr Oncol 1996;26:75-80.
25. Duarte RJ, Denes FT, Cristofani LM, Odone-Filho V, Srougi M. Further experience with laparoscopic nephrectomy for Wilms'

tumour after chemotherapy. BJU Int 2006;98:155-9.

26. D'Angio GJ, Evans AE, Breslow N, Beckwith B, Bishop H, Feigl P, *et al* . The treatment of Wilms' tumor: Results of the National Wilms' Tumor Study. Cancer 1976;38:633-46. [↑](#)
27. D'Angio GJ, Evans AE, Breslow N, Beckwith B, Bishop H, Farewell V, *et al* . The treatment of Wilms' tumor: Results of the Second National Wilms' Tumor Study. Cancer 1981;47:2302-11.
28. D'Angio GJ, Breslow N, Beckwith JB, Evans A, Baum H, deLorimier A, *et al* . Treatment of Wilms' tumor: Results of the Third National Wilms' Tumor Study. Cancer 1989;64:349-60.
29. Tournade MF, Com-Hougue C, Voute PA, Lemerle J, de Kraker J, Delemarre JF, *et al* . Results of the sixth International Society of Pediatric Oncology Wilms tumor trial and study: A risk-adapted therapeutic approach in Wilms tumor. J Clin Oncol 1993;11:1014-23.
30. Tournade MF, Com-Nougui C, de Kraker J, Ludwig R, Rey A, Burgers JM, *et al* . Optimal duration of preoperative therapy in unilateral and nonmetastatic Wilms' tumor in children older than 6 months: Results of the ninth International Society of Pediatric

Oncology Wilms' tumor trial and study. J Clin Oncol 2001;19:488-500.

31. Lemerle J, Voute PA, Tournade MF, Rodary C, Delemarre JF, Sarrazin D, *et al* . Effectiveness of preoperative chemotherapy in Wilms' tumor: Results of an International Society of Paediatric Oncology (SIOP) clinical trial. J Clin Oncol 1983;1:604-9.
32. Green DM, Breslow NE, Beckwith JB, Ritchey ML, Shamberger RC, Haase GM, *et al* . Treatment with nephrectomy only for small, stage I/favorable histology Wilms' tumor: A report from the National Wilms' Tumor Study Group. J Clin Oncol 2001;19:3719-24.
33. Dome JS, Cotton CA, Perlman EJ, Breslow NE, Kalapurakal JA, Ritchey ML, *et al* . Treatment of anaplastic histology Wilms' tumor: Results from the fifth National Wilms' Tumor Study. J Clin Oncol 2006;24:2352-8.
34. de Kraker J, Graf N, Tinteren H, Pein F, Sanstedt B, Godzinski J, *et al* . Reduction of postoperative chemotherapy in children with stage I intermediate risk and anaplastic Wilms' tumour (SIOP 93-01 trial): A randomized controlled trial. Lancet 2004;364 : 1229-35.

35. Pritchard J, Imeson J, Barnes J, Cotterill S, Gough D, Marsden HB, *et al* . Results of the United Kingdom Children's Cancer Study Group (UKCCSG) First Wilms' Tumour Study (UKW-1). *J Clin Oncol* 1995;13:124-33.
36. Mitchell C, Jones PM, Kelsey A, Vujanic GM, Marsden B, Shannon R, *et al* . The Treatment of Wilms' Tumour: Results of the United Kingdom Children's Cancer Study Group (UKCCSG) Second Wilms' Tumour Study. *Br J Cancer* 2000;83:602-8.
37. Green DM, Breslow NE, Beckwith JB, Finklestein JZ, Grundy PE, Thomas PR, *et al* . Comparison between single-dose and divided-dose administration of dactinomycin and doxorubicin for patients with Wilms' tumor: A report from the National Wilms' Tumor Study Group. *J Clin Oncol* 1998;16: 237-45.
38. Green DM, Finklestein JZ, Tefft ME, Norkool P. Diffuse interstitial pneumonitis after pulmonary irradiation for metastatic Wilms' tumor: A report from the National Wilms' Tumor Study. *Cancer* 1989;63:450-3.
39. Montgomery BT, Kelalis PP, Blute ML, Bergstralh EJ, Beckwith JB, Norkool P, *et al* . Extended follow-up of bilateral Wilms' tumor: Results of the National Wilms' Tumor Study. *J Urol* 1991;146:514-8.

40. Horwitz JR, Ritchey ML, Moksness J, Breslow NE, Smith GR, Thomas PR, *et al* . Renal salvage procedures in patients with synchronous bilateral Wilms' tumors: A report from the National Wilms' Tumor Study Group. J Pediatr Surg 1996;31:1020-5.
41. Fuchs J, Wunsch L, Flemming P, Weinel P, Mildemberger H. Nephron-sparing surgery in synchronous bilateral Wilms' tumors. J Pediatr Surg 1999;34:1505-9.
42. Kist-van Holthe JE, Ho PL, Stablein D, Harmon WE, Baum MA. Outcome of renal transplantation for Wilms' tumor and Denys-Drash syndrome: A report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Transplant 2005;9:305-10.
43. Bhagwat R, Kurkure P, Iyer K, Biswas G, Siddique N, Padhye B, *et al* . Is anthracycline based chemotherapy for all stages of Wilms Tumour (WT) a practical compromise for better outcome in developing countries? SIOP XXXVI meeting Abstracts PJ024. Pediatr Blood Cancer 2005;45:530.
44. Dome JS, Liu T, Krasin M, Lott L, Shearer P, Daw NC, *et al* . Improved survival for patients with recurrent Wilms tumor: The experience at St. Jude Children's Research Hospital. J Pediatr Hematol Oncol 2002;24:192-8.

45. Grundy P, Breslow N, Green DM, Sharples K, Evans A, D'Angio GJ. Prognostic factors for children with recurrent Wilms' tumor: Results from the Second and Third National Wilms' Tumor Study. *J Clin Oncol* 1989;7:638-47.
46. Campbell AD, Cohn SL, Reynolds M, Seshadri R, Morgan E, Geissler G, *et al* . Treatment of relapsed Wilms' tumor with high-dose therapy and autologous hematopoietic stem-cell rescue: The experience at Children's Memorial Hospital. *J Clin Oncol* 2004;22:2885-90.
47. Coppes MJ, Arnold M, Beckwith JB, Ritchey ML, D'Angio GJ, Green DM, *et al* . Factors affecting the risk of contralateral Wilms' tumor development: A report from the National Wilms' Tumor Study Group. *Cancer* 1999;85:1616-25.
48. Paulino AC, Thakkar B, Henderson WG. Metachronous bilateral Wilms' tumor: The importance of time interval to the development of a second tumor. *Cancer* 1998; 82:415-420.
49. Green DM, Grigoriev YA, Nan B, Takashima JR, Norkool PA, D'Angio GJ, *et al* . Congestive heart failure after treatment for Wilms' tumor: A report from the National Wilms' Tumor Study group. *J Clin Oncol* 2001;19:1926-34.
50. Marilia Fornaciari *et al*, Prognosis for patients with unilateral

Wilms Tumour in RIO de Jaeniro, Brazil 1999 – 2000,
Rev.Sau'de Publica 2005-35(5)